AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0035] on page 9 of the Substitute Specification filed January 21, 2004 with the following paragraph:

~~Figure 11b shows~~ Figures 11B and 11C show results of a second experiment demonstrating that epithelial PAR2 receptors in mouse bronchi are regulated by a rapid turnover following desensitisation to trypsin. ~~(a)~~ (11B) Responsiveness to trypsin (0.3 U/ml) recovered to approximately 70% of control at 45 minutes from the zero recovery time (the time at which trypsin caused no response after the desensitising concentration of trypsin 0.3 U/ml) was washed from the bath; see Examples). Time control responses to trypsin at 15, 45, 80 and 120 minute recovery were not significantly different from the initial control. ~~(b)~~ (11C) The recovery of trypsin sensitivity at 45 minutes was abolished by the protein trafficking inhibitor, brefeldin A (10 μM) and the translation inhibitor cycloheximide (70 μM ~~12M~~). Both compounds had no effect on time control responses to trypsin. Values are mean [[t]] ± s.e. mean from 3-12 experiments (shown in parentheses). ($p<0.01$).

Please replace paragraph [0130] on page 39 of the Substitute Specification filed January 21, 2004 with the following paragraph:

Mouse bronchi were prepared as described in Example 1. Recovery of PAR2-mediated relaxation to trypsin following desensitization to the compound was then measured. The results, presented in Figures 11a and 11B and C ~~11b~~, showed that bronchial PAR2s were replaced very rapidly following activation with trypsin. Thus. in each experiment, complete recovery of maximum relaxation to 5 trypsin occurred 30 min after an initial desensitising concentration of trypsin. This recovery was abolished by the protein trafficking inhibitor brefelden A(10 μM) or the protein synthesis inhibitor cyclobeximide. The data show that PAR2s were rapidly replaced after activation with trypsin, since relaxation to trypsin returned to near-control levels within 45 minutes after the tissue was desensitised to trypsin. This complete and rapid recovery was abolished by the protein trafficking inhibitor, brefeldin A (10 μM ~~AM~~) and the translation inhibitor, cycloheximide (70μM; Figure 11C ~~11b~~). Equally rapid turnover of cloned PAR2 expressed in selected cell lines has been shown to be dependent on both de novo synthesis of new protein as well as trafficking of preformed receptors from intracellular pools. These data imply that new, fully intact PAR2s are vital for normal functioning of the airways.

Please replace paragraph [0169] on page 52 of the Substitute Specification filed January 21, 2004 with the following paragraph:

Since enzymatic activation of PARs is irreversible, rapid resensitisation mechanisms are critical for the maintenance of tissue responsiveness to PARactivating proteases. Turnover of cloned PAR1 expressed in selected cell lines has been shown to be rapid and dependent on both *de novo* synthesis of new protein as well as trafficking of performed receptors from intracellular pools (Dery *et al,* 1998; Bohm *et al,* 1996). The data generated herein show that in the mouse bronchi, PAR2-mediated relaxations returned after 45 min following desensitisation to trypsin (Figure 11 B ~~b~~). This recovery was abolished by the protein trafficking inhibitor, brefeldin A (10 μM) or the translation inhibitor, cycloheximide (70 μM; Figure 11C ~~11b~~). These findings, together with the demonstration here that PAR2 immunoreactivity was often localised in discrete cytoplasmic regions of airway epithelial cells (Figure 26), support the concept of rapid PAR2 turnover from intracellular stores in airway epithelium. Furthermore, the inventors were unable to demonstrate specific localisation of PAR2 mRNA in mouse bronchi using *in situ* hybridisation whilst readily detecting PAR2 mRNA in the same tissue via reverse transcription-polymerase chain reaction. The apparent discrepancy between these findings could be explained by the immunohistochemical demonstration of intracellular stores of PAR2 (Figure 26) which are continually replenished by translation of stable message of low transcript number. Thus, the capacity of airway epithelial cells *in situ* to rapidly recover their sensitivity to PAR2 agonists following receptor desensitisation supports a role for epithelial PAR2 in bronchoprotection.

Please replace paragraph [0171] on page 52 of the Substitute Specification filed January 21, 2004 with the following paragraph:

Importantly, the inventors have demonstrated here that SLIGRL-NH_2 (SEQ ID NO:2) is a highly effective inhibitor of bronchoconstriction *in vivo.* Thus, a 30 sec exposure to an aerosol of a 0.1 mg/ml ~~solutio~~ solution of SLIGRL-NH_2 (SEQ ID NO:2), but not the scrambled peptide sequence LSIGRL-NH_2 (SEQ ID NO:4) caused inhibition (50-70%) of 5-hydroxytryptamine (5-HT)-induced changes in airway resistance (R_L) and dynamic compliance (C_{dyn}) in anaesthetised rats ~~(Figure 11 b)~~. This effect of SLIGRL-NH_2 (SEQ ID NO:2) could be functionally antagonised by higher doses of 5-HT.